REMARKS

I. Status of Claims

Claims 17-22 and 24-30 are pending in the present application. Claims 1-16 and 23 are canceled. Claim 29 is withdrawn.

II. Rejection under 35 U.S.C. § 103(a)

Claims 17-19, 21, 22 and 25 are rejected under §103(a) as allegedly being unpatentable over Constantino *et al.* (*Vaccine* 10:691-698, 1992) ("Constantino") in view of Seid Jr. et al. (US 7,188,757) ("Seid") and O'Hagan (J. Pharm. Pharmaco. 50: 1-10, January 1998) ("Hagan").

Applicants respectfully traverse the rejection and its supporting remarks.

1. *No reasonable expectation of success*

The Examiner has not established a *prima facie case* of obviousness as the Examiner has not show that one of skill in the art would have had a reasonable expectation of success. The Examiner has overstated the predictability of combining different vaccine components and of combining vaccine components with adjuvants. The Examiner has suggested that Seid teaches that OMVs can be combined with capsular polysaccharide based compositions into a single vaccine. However, the Examiner has not cited to any portion of Seid that actually demonstrates that such a combination works or even specifically teaches or suggests such a combination. At best, the Summary of the Invention and column 4, lines 38-45, make sweeping statements that regarding the OMVs, the purified OMP proteins and fragments thereof as a broad group may be able to be combined with other antigens such as capsular poly saccharides without clearly specifying if all such combinations are desirable or even possible. In fact, the other portions cited by the Examiner in the detailed description lead to the opposite conclusion. The first two full paragraphs of Col. 11, cited by the Examiner, only refer to combination of the proteins or peptides with capsular components – OMVs are strikingly absent. Example 1B is merely a protocol for preparing OMVs without any indication that they were to be combined with any other vaccine component. Furthermore, in Example 15 as

cited by the Examiner, the inventors do actually combine capsular polysaccharides from serogroup C with an OMP derived peptide conjugate. Again, this is very telling that the inventors did not think combining OMVs with capsular polysaccharides was desirable or even possible. The inventors had OMVs, had capsular polysaccharide conjugates and had peptides, but only tried combining the capsular polysaccharide with the peptide even though they could have at the same time tested the capsular polysaccharide with the OMVs. The fact that Seid *et al.* did not shows that Seid does not teach or suggest combining and supports the lack of predictability in the combination.

Combining vaccine components particularly from different classes, membrane vesicles versus capsular polysaccharides, can produce unpredictable results. The data in the specification clearly shows that there is unpredictability in this combination. By way of example, as is shown in Table 3 in the specification, the combination of the two antigens increases the immune response to OMV (NmB in the table) by more than 6-fold, but ***decreases*** the immune response the capsular polysaccharide component by some unknown amount (but at least more than one third). By contrast, Seid *et al.* show in table 5B that addition of the OMP peptide increases the response to the capsular polysaccharide more than 2.5-fold.

Things become even more unpredictable with the addition of an adjuvant. The Examiner asserts that O'Hagen teaches that MF59 produces a 5-50 fold increase in immune response over alum and would clearly be selected by one of skill in the art and thus would be motivated to replace the alum as used by Constantino *et al.*, but O'Hagen is merely citing the best case results as MF59 does not always produce better results than alum. And in fact, despite the glowing praise for MF59 in O'Hagen, MF59 is not yet in any approved vaccine in the United States. Further, contrary to the Examiner's assertion, the MF59 actually produces a lower immune response against the OMV component as shown by Table 3 in the specification. Thus, one cannot say that one of skill in the art would routinely select MF59 over alum and one cannot say that one of skill in the art would expect that MF59 would work better than alum especially given that it, in fact, works less well with one of the two claimed components.

2. *Inappropriate Obvious to Try*

Constantino *et al.* used alum as an adjuvant so the Examiner must first posit some undisclosed flaw in Constantino that would motive one of skill in the art to try a different adjuvant. Vaccines are not like a predictable mechanical art where there may be a general motivation to improve even absent express statement of such motivation, but there absolutely is not a general motivation to increase the immunogenicity to vaccines to ever increasing levels. The immune system can be overstimulated which can cause averse reactions so a skilled practitioner will only seek to improve immunogenicity of a vaccine where there is demonstrated need. Even if one of skill in the art were motivated to replace the alum in the oligosaccharide composition of Constantino *et al.*, this is at best a suggestion that it would be obvious to try among all the available adjuvants to determine which, if any, would work better than aluminum hydroxide given that MF59 is not the only other adjuvant in existence. The Federal Circuit in *In re O'Farrell* stated that:

> "The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication as to which of many possible choices is likely to be successful.... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidelines as to the particular form of the claimed invention or how to achieve it." In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

Thus, if one of skill in the art was motivated to increase the antigenicity by replacing the alum adjuvant of the composition of Constantino *et al.*, the person of ordinary skill in would try from a large number of available adjuvants. By way of example, Seid '513 from col. 12, line 37 to col. 13, line 2 identifies at least six classes of adjuvants that includes seventeen different adjuvants.

> Adjuvants may also be used to enhance the effectiveness of the vaccines. Adjuvants can be added directly to the vaccine compositions or can be administered separately, either concurrent with or shortly after, vaccine administration. Such adjuvants include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide,

> aluminum phosphate, aluminum sulfate, etc.; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (International Publication No. WO 90/14837), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE (see below), although not required) formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, Mass.), (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi.TM. adjuvant system (RAS), (Ribi Immunochem, Hamilton, Mont.) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL+CWS (Detox.TM.); (3) saponin adjuvants, such as Stimulon.TM. (Cambridge Bioscience, Worcester, Mass.) may be used or particle generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freunds Adjuvant (CFA) and Incomplete Freunds Adjuvant (IFA); (5) cytokines, such as interleukins (IL-1, IL-2, etc.), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc.; and (6) other substances that act as immunostimulating agents to enhance the effectiveness of the composition.
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> Muramyl peptides include, but are not limited to, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acteyl-normuramyl-L-alanyl-D-isogluatme (nor-MDP), N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn -glycero-3-huydroxyphosphoryloxy)-ethylamine (MTP-PE), etc.

Thus, from this list alone, one of skill in the art would have seventeen adjuvants to test to see which, if any, may increase the antigenicity of the composition of Constantino *et al.* to better than that provided by the adjuvant already in the composition.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 17-19, 21, 22, and 25 under §103(a).

III. Rejection under 35 U.S.C. § 103(a)

Claim 24 is rejected under §103(a) as being unpatentable allegedly over Constantino *et al.* (*Vaccine* 10:691-698, 1992) ("Constantino") in view of Seid Jr. et al. (US 7,188,757) ("Seid") and O'Hagan (J. Pharm. Pharmaco. 50: 1-10, January 1998) ("Hagan") in further view of Seid J. et al. (US 6,638,513).

As discussed above, the Examiner has not established a *prima facie* case of obviousness as there is no reasonable expectation of success for the particular combination claimed. The addition of Seid '513 fails to remedy the expectation of success as Seid '513 fails to combine serogroup B OMVs with a capsular polysaccharide from serogroup C and does not use MF59 in any form.

Seid '513 teach polylactic acids as a possible alternative carrier, but state a preference for CRM_{197} and never actually using polylactic acids. Thus, the Examiner has provided no reason why one of skill in the art would want to use polylactic acids as the carrier rather than CRM_{197}.

Furthermore, this proposed modification would render the composition of Constantino unsuitable for the desired use. Constantino *et al.* state in the introduction on page 691 that the protein conjugate is specifically added to induce an immune response in very young children who do not produce a good antibody response to the capsular polysaccharide without the protein. As the MPEP 2143.01(V) states "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." Replacing the CRM197 carrier of Constantino *et al.* with a polylactic acid carrier would render the composition unsatisfactory to such very young children as the toxoid protein is needed for the immune response in such children, so there can be no motivation to combine.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 26 under §103(a).

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. 223002100100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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